Extracardiac control of embryonic cardiomyocyte proliferation and ventricular wall expansion.

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Public Summary:
This study evaluated how the signaling protein IGF2 influences heart development. The study used genetic strategies to identify the tissue source of IGF2 in heart development, defined two different processes that sequentially control IGF2 activity, and showed how these two processes are coordinated with other developmental events that occur in the embryo.

Scientific Abstract:
AIMS: The strategies that control formation of the ventricular wall during heart development are not well understood. In previous studies, we documented IGF2 as a major mitogenic signal that controls ventricular cardiomyocyte proliferation and chamber wall expansion. Our objective in this study was to define the tissue source of IGF2 in heart development and the upstream pathways that control its expression. METHODS AND RESULTS: Using a number of mouse genetic tools, we confirm that the critical source of IGF2 is the epicardium. We find that epicardial Igf2 expression is controlled in a biphasic manner, first induced by erythropoietin and then regulated by oxygen and glucose with onset of placental function. Both processes are independently controlled by retinoic acid signalling. CONCLUSIONS: Our results demonstrate that ventricular wall cardiomyocyte proliferation is subdivided into distinct regulatory phases. Each involves instructive cues that originate outside the heart and thereby act on the epicardium in an endocrine manner, a mode of regulation that is mostly unknown in embryogenesis.